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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CLARK, SARA E	

ART UNIT	PAPER NUMBER
4121	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,557	SOLOMON, MICHAEL	
	Examiner	Art Unit	
	SARA E. CLARK	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is a 35 U.S.C. 371 (national stage) application of PCT/US04/18985, filed 6/16/2004, which claims benefit of priority to provisional applications 60/478,764, filed 6/16/2003, and 60/496,621, filed 8/20/2003. Claims 1-26 are pending.

Priority

1. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

2. However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e). The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The disclosure of the prior-filed application, provisional application No. 60/478,764, filed 6/16/2003, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the disclosure of provisional application No. 60/478,764 contains no data indicating that the claimed compounds are capable of functioning in the claimed methods. However, provisional application 60/496,621, filed 8/20/2003, does contain such data. Therefore, claims 1-26 are entitled to a priority date of 8/20/2003.

Election/Restrictions

3. Applicant's election with traverse of Group II, claims 11-25, in the reply filed on 2/17/2009 is acknowledged. The traversal is on the ground(s) that formulae IVa, IVb, Va, Vb, and compound 1 of Group II fall within the scope of formulae II, IIIa, or IIIb of Group I. This is found persuasive, and the restriction requirement is withdrawn. The requirement to elect a species, however, is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

4. All references submitted on the IDS dated 2/17/2007 have been considered.

Claim Rejections - 35 USC § 112 First Paragraph

Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using compound 1 to treat insomnia and sleep maintenance insomnia, does not reasonably provide enablement for the broad, diverse genus of compounds claimed, of which compound 1 represents a species, or for the divergent array of sleep disorders claimed. The specification does not enable a person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate with the scope of these

claims. MPEP 2164.01(a), citing *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), sets out the factors to determine whether experimentation is undue, which include:

(A) The breadth of the claims. The claims are expansive beyond what the specification enables in two ways. First, claims 1-22 are drawn to generic formulae encompassing hundreds of compounds, although only one was actually tested *in vivo*. Second, claims 1-4, 6-9, 11-14, 16-19, and 21-22 are drawn to sleep disorders with different etiologies, from circadian rhythm disorders to sleep apnea to night terrors, when the data shows only increases in non-REM sleep (NREM) and longest uninterrupted sleep bout (LUSB). The specification notes that these demonstrate the tested compound's potential for treating insomnia and sleep-maintenance insomnia, respectively (p. 42), but no further data is presented which suggests the efficacy of the tested compound for treating other sleep disorders. In sum, the claimed compounds and claimed disorders are far broader than the disclosure reasonably supports.

(B) The nature of the invention. The heart of the invention is the induction of sleep using a compound that is structurally related to anti-psychotic and anti-depressive agents known to have sedative side effects, such as loxapine, clozapine, and olanzapine. This is a fairly densely populated field, in which changes in one functional group or stereochemistry alone can have powerful and even dangerous effects. This weighs strongly against the enablement of a large genus of compounds on the basis of only one species.

(C) The level of predictability in the art. The multiplicity of effects a given psychotropic drug can have often become evident only after the drug has been in wide use for many years, making the art of psychopharmacology unpredictable. For example, the tricyclic antidepressant amitriptyline, which has very close structural similarity to the claimed genus of compounds, is also known in the treatment of insomnia (see, e.g., Eddy et al. 1999, abstract and p. 5). At the same time, tricyclic antidepressants, so named because they contain the same "tricyclic" moiety of the claimed genus, may induce or worsen certain sleep disorders, such as restless leg syndrome (see, e.g., Touchon 1995, abstract). Restless leg syndrome is identified in the disclosure (p. 27, lines 12) as one of the conditions within the broad genus of sleep disorders recited in claims 1-3, 5-8, 10-13, 15-18, and 20-26, and specifically recited in claims 4, 9, 14, and 19. In other words, compounds with close structural similarity to those claimed are known to both ameliorate and aggravate certain sleep disorders, depending on the identity of the drug; the patient's age and mental health status (depressed or non-depressed); tobacco, alcohol, exercise, and eating habits; and other factors.

(D) The amount of direction provided by the inventor. The specification is exceptionally thorough in enumerating all the possible substituents and structures the claimed compounds might have, the formulations and forms in which it might be administered, and an exhaustive list of the myriad disorders it might be used to treat. "Might" is the operative word here: only in the last two pages of the forty-page specification is there an actual reduction to practice, in which one embodiment of the

compound is administered to test animals. Considerable direction is given, but only one compound is shown to produce the desired effect.

(E) The existence of working examples. The specification discloses one working example with test animals (rats), but none with humans, recited in claims 2, 7, 12, 17, and 26 as the intended subjects to be treated. Showing that one compound produces the desired effect does not enable the entire genus. Showing that it induces sleep in rats does not enable the broad genus of sleep disorders that generally afflict only humans.

(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. How to use the invention in a clinical setting is not well-developed in the disclosure, such that substantially more than routine experimentation would be required to practice the invention commensurate with the scope of the claims. For example, Andersen et al. (WO2000/037081, published 6/29/2000, p. 2) found that the half-life for ReN 1869 (compound 1) is so short, there is a need to control the release of the compound in such a manner that an effective concentration in the blood can be maintained over an extended period of time, such as during the night. These observations lead one skilled in the art to conclude that an undue amount of experimentation is required to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 112 First Paragraph

Scope of Enablement

7. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts, does not reasonably provide enablement for pharmaceutically acceptable solvates or hydrates. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. MPEP 2164.01(a), citing *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), sets out the factors to determine whether experimentation is undue, which include:

(A) The breadth of the claims. By encompassing any solvates or hydrates of compounds of formula II, the scope of the claims is broader than the disclosure.

(B) The nature of the invention. The nature of the invention is methods of treating sleep disorders using the genus of compounds encompassed by formula II; specifically, the elected compound 1, 1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

(C) The level of predictability in the art. Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product.

Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs, solvates, and hydrates are not so common so as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization

Crystalline solids can exist in the form of polymorphic forms, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during

various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al. 2001, 3-26, abstract). In further discussing the predictability of the formation of solvates, Vippagunta et al. disclose that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (p. 18). Therefore, for these reasons, the state of the prior art is regarded as unpredictable.

(D) The amount of direction provided by the inventor. No guidance is presented in the specification for the preparation of solvates or hydrates of compounds of formula II. The specification only discloses that “[c]ertain compounds and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof" (p. 32, lines 17-18). The direction is limited to the disclosure that certain compounds can exist in solvated form; however, it is not discussed which specific compounds can exist in this form, or how to prepare them. Additionally, preferred embodiments and examples are silent as to whether the claimed compounds are administered in the form of solvates or hydrates.

(E) The existence of working examples. The disclosure provides no working examples for the preparation of solvates.

(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. While the level of skill in the pharmaceutical arts is high, it would require undue experimentation to prepare *any* solvate or hydrate of the compounds of formula II. The science of crystallization has evolved such that, without guidance or working examples in the specification, one of skill in the art would conclude that an undue amount of experimentation is required to practice the full scope of the claimed invention; thus, the claims lack enablement. This rejection can be overcome by deletion of the words "solvate or hydrate thereof" from claims 1, 6, 11, 16, and 23.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen et al. (Eur. J. Pharm. 435, 23-57, Jan. 18, 2002) in view of Skrumsager et al. (J. Clin. Pharm. 43(1): 66-73, Jan. 2003) and Richardson et al. (J. Clin. Pharm. 22(5) 511-515, Oct. 2002).

10. Olsen et al. teach a method of using 1-(3-(10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid (also known as ReN 1869, corresponding to compound 1 of the claimed invention) to treat neurogenic pain and inflammation in human patients, and show that analgesic and anti-inflammatory

effects of ReN 1869 are due mainly to its activity as a histamine H1 receptor antagonist (p. 53). While compound 1 is thus known as a pharmaceutical administered to human subjects with therapeutic effects, Olsen et al. do not teach the use of ReN 1869 specifically to treat sleep disorders.

Skrumsager et al. evaluated the safety and pharmacokinetics of ReN 1869 in healthy human subjects, and observed that the most frequently reported side effects of ReN 1869 included fatigue and somnolence (abstract). However, Skrumsager et al. sought to explore other properties of ReN 1869, rather than its potential as a sedative.

The motivation to administer ReN 1869 to humans as a therapeutic agent, as taught by Olsen et al., to induce sleep, as suggested by the ReN 1869-induced somnolence observed by Skrumsager et al., can be found in Richardson et al., which teaches that first-generation H1 antihistamines are well-known to produce a sedative effect, the basis for their use as nonprescriptive remedies for insomnia (abstract). Together, these teachings would have led one of ordinary skill in the art to arrive at the inventions recited in claims 1, 2, 4-7, 9-12, 14-17, and 19-26, namely, the administration of ReN 1869 to human patients to induce somnolence and treat insomnia. This also reads on claims 3, 8, 13, and 18, drawn to the treatment of circadian rhythm adjustment disorders, defined in the specification to include difficulty adjusting to a new circadian rhythm due to jet lag or shift work (p. 27, lines 19-20), since inducing somnolence will achieve the treatment of this condition as well.

Therefore, the administration of ReN 1869 (corresponding to elected compound 1) to humans as a therapeutic agent, as taught by Olsen et al., to induce somnolence as

taught by Skrumsager et al., due to its activity as a sedating histamine H1 antagonist as taught by Richardson et al., as a novel agent to induce sleep, thereby treating sleep disorders, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

10. Claims 1-26 are rejected.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEC

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121